

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

[Docket No. 2004D-0377]

Copy Date 10-19-05

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**International Conference on Harmonisation; Guidance on E14 Clinical  
Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for  
Non-Antiarrhythmic Drugs; Availability**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

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**SUMMARY:** The Food and Drug Administration (FDA) is announcing the availability of a guidance entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs." The guidance was prepared under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guidance provides recommendations to sponsors concerning clinical studies to assess the potential of a new drug to cause cardiac arrhythmias, focusing on the assessment of changes in the QT/QTc interval on the electrocardiogram as a predictor of risk. The guidance is intended to encourage the assessment of drug effects on the QT/QTc interval as a standard part of drug development and to encourage the early discussion of this assessment with FDA.

**DATES:** Submit written or electronic comments on agency guidances at any time.

**ADDRESSES:** Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers  
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Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. Submit written requests for single copies of the guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, or the Office of Communication, Training and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. The guidance may also be obtained by mail by calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800. Send one self-addressed adhesive label to assist the office in processing your request. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

**FOR FURTHER INFORMATION CONTACT:**

*Regarding the guidance:* Douglas C. Throckmorton, Center for Drug Evaluation and Research (HFD-1), Food and Drug Administration, 5600 Fishers Lane, Rockville MD, 20857, 301-594-5400.

*Regarding the ICH:* Michelle Limoli, Office of International Programs (HFG-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4480.

**SUPPLEMENTARY INFORMATION:**

**I. Background**

In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical

development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development among regulatory agencies.

ICH was organized to provide an opportunity for tripartite harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission; the European Federation of Pharmaceutical Industries Associations; the Japanese Ministry of Health, Labour, and Welfare; the Japanese Pharmaceutical Manufacturers Association; the Centers for Drug Evaluation and Research and Biologics Evaluation and Research, FDA; and the Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and the IFPMA, as well as observers from the World Health Organization, Health Canada, and the European Free Trade Area.

In the **Federal Register** of September 13, 2004 (69 FR 55163), FDA published a notice announcing the availability of a draft tripartite guidance entitled "E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs." The notice gave interested persons an opportunity to submit comments by December 13, 2004. In response to a request for additional time to comment, FDA reopened the

comment period until February 18, 2005 (70 FR 823, January 5, 2005). On April 11 and 12, 2005, FDA, the Drug Information Association, and the Heart Rhythm Society cosponsored a public meeting to discuss the draft guidance. Comments received at the meeting were made available to the Efficacy Expert Working Group. After consideration of the comments received and revisions to the guidance, a final draft of the guidance was submitted to the ICH Steering Committee and endorsed by the three participating regulatory agencies in May 2005.

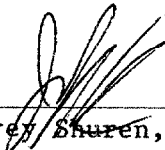
The guidance provides guidance on the design, conduct, analysis and interpretation of clinical studies to assess the potential of a new drug to cause cardiac arrhythmias, focusing on the assessment of changes in the QT/QTc interval on the electrocardiogram as a predictor of risk. The guidance is intended to encourage the assessment of drug effects on the QT/QTc interval, along with the collection of adverse cardiac events related to arrhythmias, as a standard part of drug development, and to encourage the early discussion of this assessment with the FDA. The goal of such discussions is to reach a common understanding of the effects as early in development as practical, with the goal of enhancing the efficiency of data collection later in drug development. The guidance incorporates the following changes: (1) A fuller discussion of the factors that influence the clinical assessment of drug effects on the QT interval and (2) an adjustment in the statistical analysis of QT interval data obtained as a part of early thorough QT assessment.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative

### III. Electronic Access

Persons with access to the Internet may obtain the document at <http://www.fda.gov/ohrms/dockets/default.htm>, <http://www.fda.gov/cder/guidance/index.htm>, or <http://www.fda.gov/cber/publications.htm>.

Dated: 10/12/05  
October 12, 2005.

  
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Jeffrey Shuren,  
Assistant Commissioner for Policy.

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